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SMALL VOLUME RESUSCITATION OF HYPOVOLEMIC SHOCK

Annual Report

1 Feb 87 - 31 Jan 88

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March 1, 1988

Supported by

U.S. Army Medical Research and Development Command

Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86-C-6115

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: University of California School of Medicine; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): Department of Human Physiology Davis, CA 95616	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: Contract No. DAMD17-86-C-6115
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
62772A	3S1-62772A874	AB	128

11. TITLE (Include Security Classification)

Small Volume Resuscitation of Hypovolemic Shock

12. PERSONAL AUTHOR(S)

Kramer, George C., Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual Report	FROM 2/1/87 TO 1/31/88	1988 March 1	33

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	04		RA IT; Lab animals; Rats; Sheep; Hypertonic resuscitation; Peripheral vein injections
06	01		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Studies were performed to evaluate the importance of the dextran component in hypertonic saline/dextran. Hemorrhaged awake sheep were resuscitated with 7.5% NaCl alone (HS) 7.5% NaCl/6% dextran and 7.5% NaCl/24% dextran. There was a dose related effect between the dextran infused and the improvement in blood pressure, cardiac output and volume expansion. These differential responses were apparent immediately post resuscitation and became larger during the first 2-3 hours post resuscitation. Multiple bolus injections of ~1 ml/kg each of 7.5% NaCl/6% dextran 70 appeared to be safe and effective for resuscitation of hemorrhage. Only 2-3 40 ml injections were required to maintain cardiovascular function at baseline levels. Higher concentrations of salt (28% NaCl) with 24% dextran were shown to effectively resuscitate a 1.2 - 1.8 ℓ blood loss in volumes as small as 40 ml.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICA: Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL: Mrs. Virginia M. Miller	22b. TELEPHONE (Include Area Code): 301/663-7325

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY

TABLE OF CONTENTS

Foreword

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

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Summary

Studies on unanesthetized sheep were performed to evaluate the effectiveness of hypertonic saline dextran formulations. Based on presented data we conclude:

The addition of dextran to hypertonic saline increases plasma volume expansion and cardiac output in the early post-resuscitation time period.

Hypertonic 7.5% NaCl, 6% dextran 70 solution can be effectively given in multiple small doses of ~1 ml/kg.

1. Statement of Problem

Recent animal investigations in our lab (1,2,3) and those of others (4,5,6) have established that small volume infusions of hypertonic saline can effectively restore cardiovascular function after hypovolemic shock. It is our overall goal to extend our experience and knowledge of small volume resuscitation. We must establish the most effective way to utilize hypertonic resuscitation and determine its limits and possible dangers. Most important is to better understand the physiologic and biochemical mechanism of its beneficial effects. Our specific aims are:

*1) Evaluate the importance of adding colloid to hypertonic resuscitation.

2) Evaluate the possibility of using peripheral vein access for hypertonic resuscitation.

*3) Determine the effectiveness and safety of multiple bolus injections of hypertonic saline.

4) Use NMR to measure intracellular energy stores during hemorrhage in skeletal muscle, kidney, and liver.

5) Use NMR to evaluate the metabolic effectiveness of hypertonic resuscitation regimens.

6) Measure the distribution of cardiac output during hypertonic resuscitation.

7) Use hypertonic resuscitation in dehydrated animals.

* indicates work performed during year 02 and presented in this report

2. Background

Basic and clinical research stimulated by World Wars I and II established the basis for current treatment of hypovolemic shock as 1) control of hemorrhage and 2) restoration of vascular volume (7). A hemorrhaged soldier arriving at a field hospital in Vietnam was given definitive care - prompt surgical control of bleeding and intravenous infusions of physiological salt solution and/or blood as needed (8). Despite the availability of effective resuscitation therapy in hospitals exsanguination remained the main cause of mortality, being responsible for 50% of all deaths even with a highly efficient system of rapid helicopter evacuation (9,10). A recent model analysis based on Vietnam casualty statistics concluded "for there to be significant improvement in combat casualty care there must be a renewed emphasis on field medical care, with special attention to management of hemorrhage" (10). Successful field resuscitation has been limited by the large volumes required of solutions of crystalloid (2-4x shed blood volume) and colloid (1-1-1/2x shed blood). Logistically feasible field therapies are needed which will reestablish near normal cardiovascular function, and protect against the deleterious metabolic alterations of tissue ischemia.

A novel approach to resuscitation is suggested by the studies of Rocha e Silva and his colleagues (4,5) in which hemorrhaged dogs were successfully resuscitated with a small bolus infusion of hypertonic saline. A 2400 milli-osmolar solution of sodium chloride equal in volume to only 10% of shed blood rapidly returned cardiac output and blood pressure to normal (4). These significant and rapidly beneficial effects of hypertonic infusions have been generally verified in our studies of hemorrhage and resuscitation of the unanesthetized sheep (1,2). Improved survival has been demonstrated in an anesthetized dog by Rocha e Silva and more recently in conscious swine by Traverso et al. (4,6). Resuscitation with equal volumes of 1200 mosm and 4800 mosm sodium chloride were not as effective as with 2400 mosm. The exact mechanisms of hypertonic resuscitation remain undefined but are at least partly due to plasma

volume expansion subsequent to a cellular/extracellular fluid shift and a significant reduction in peripheral resistance. In addition, stimulation of a pulmonary osmoreceptor may initiate a reflex decrease in venular capacitance, thus effectively increasing cardiac output to normal levels despite blood volumes less than normal (5).

We have shown that the initial rapid improvement in cardiovascular function is a function of the increased osmolality per se and does not require either sodium or chloride (11). Figure 1 shows a study in which we performed a screening evaluation of the effectiveness of five different hypertonic solutions.

Mean arterial pressure is plotted for baseline conditions, during 2 hours of hemorrhage (blood loss = 40-45 ml/kg) and for 3 hours after a 4 ml/kg bolus of 2400 mosm solutions of sodium chloride (NaCl); sodium acetate-sodium chloride mix 50:50 (Acetate); Glucose; Mannitol-sodium chloride mix 60:40; and sodium-bicarbonate (Bicarb). Clearly all solutions rapidly returned cardiac output to normal levels within minutes of bolus injection. Thereafter, blood pressure slowly declined with all solutions. The most effective solution was 2400 mosm saline which caused rapid and full restoration of cardiovascular function, but the improvement was only transitory.

At this time we began to consider the possibility of adding a hyperoncotic colloid to the formulation. We reasoned that the hypertonic sodium chloride would pull water out of the cell while a hyperoncotic colloid would selectively partition this water in the vascular space. This idea was suggested by our earlier work on dextran 70 in burn resuscitation in which we found dextran to be a highly efficient plasma volume expander associated with a good cardiovascular response (12). In a detailed study (Figure 2) we compared a mixture of hypertonic sodium chloride mixed with 6% dextran 70, (HS-Dex) against hypertonic saline alone (HS) and 6% dextran 70 in normal saline (Dex) and no resuscitation. Hypertonic saline-dextran (NaCl-Dex)

resulted in significantly higher values of sustained cardiac output, mean arterial pressure, and measured plasma volume while the total peripheral resistance was lower when compared to hypertonic saline alone or dextran alone. In short, while the hyperosmotic solutions caused a large and immediate improvement in cardiovascular function the addition of the dextran was required to sustain the effectiveness.

In the past year we have completed a further analysis of the importance of the addition of dextran. This was performed in response to Army and FDA requests for compelling preclinical data on the efficacy of the dextran component. We have also examined the effectiveness of infusing smaller (~1ml/kg) multiple boli of hypertonic saline dextran. These studies are presented in this annual report.

3. Rationale

The overall rationale of our study is to evaluate the efficacy and safety of small volume hypertonic resuscitation in experimental animals. Specifically, we will quantitate the cardiovascular response and metabolic response of vital organs during shock and after therapy with different hypertonic formulations and resuscitation regimens. We believe that these experiments will establish potential clinical therapeutic regimens. It is our hope that these regimens will provide field corpsmen with a logistically feasible and effective means to stabilize cardiovascular function in wounded soldiers until definitive care at a field hospital can be provided.

4. Experimental Methods

All experimental procedures outlined below have been previously used by the investigators (1, 2, 11, 12, 13). Our laboratory is equipped for aseptic survival surgery and cardiovascular monitoring of unanesthetized and anesthetized animals.

Sheep were used to study the cardiovascular responses to different resuscitation regimens: a) effects of multiple boli infusion of hypertonic saline dextran, and b) comparisons of hypertonic saline versus hypertonic saline dextran. Sheep were anesthetized with halothane/nitrous oxide for placement of silastic catheters in the thoracic aorta and vena cava and a Swan Ganz thermodilution catheter in the pulmonary artery. Experiments on awake sheep were performed 4-7 days after surgery. Sheep offer several advantages. They are a relatively inexpensive large animal and are easy to study in the unanesthetized state. The awake sheep's cardiovascular response to hemorrhage and resuscitation is similar to man (7), and its response is more applicable than those measured in anesthetized animal preparations. At a blood pressure of 60 mm Hg and lower sheep lie down in their cages. They experience no apparent pain during hypotension, are generally lethargic but conscious for the entire experimental protocol. All sheep experiments consisted of measurements made during a 2 hr baseline period; 2 hr of hemorrhagic hypotension (50 mm Hg) maintained by bleeding without reinfusion, and 2-4 hrs of post-resuscitation monitoring.

Measured Variables: Pressures of the aorta, pulmonary artery, pulmonary wedge and right atrium were measured with P23 Gould transducers. Pressures, and heart rate were monitored on a multi-channel strip chart recorder. Cardiac output was determined by thermal dilution using an Edwards Cardiac Output Computer. Arterial blood gases and pH were measured with an Instrumentation Laboratories Blood Gas Analyzer. Arterial and mixed venous oxygen content were determined on an Instrumentation Laboratories Co-oximeter. Oxygen consumption was calculated as the average cardiac output times the difference in A-V oxygen content. Urine output was determined by continuous collection from a Foley retention catheter. Plasma and urine concentrations of Na^+, K^+ and Cl^- as well as total osmolality were measured by flame photometry, acid titration and freezing point depression respectively. Lactate was measured on protein precipitated blood samples with enzyme assay. Creatinine clearance was determined by enzymatic assays of blood and urine. Plasma volume was measured as the distribution volume of Evans Blue dye.

5. Results

a) The efficacy of the dextran component of hypertonic saline dextran

Three research groups (Davis, Letterman and Sao Paulo) have compared small volume resuscitation of hemorrhage using hypertonic saline alone (HS) versus hypertonic saline/dextran (HSD). I have summarized the four studies from these groups which deal directly with the integrated cardiovascular response of both resuscitation regimens.

1. Smith, et al. (Davis Group) "A comparison of several hypertonic solutions for resuscitation of bled sheep." Journal of Surgical Research 39:517-528, 1985.

This was the first paper which compared 4 ml/kg hypertonic 1.2 M saline alone (HS) versus hypertonic saline/6% dextran 70 (HSD). Unanesthetized sheep were bled over 2 hours to maintain arterial pressure at 50 mm Hg, bled volume = 39-44 ml/kg. After a 2 min bolus infusion sheep were followed for 3 hours. There was no statistical difference in the aortic pressure response at any time point; although with HSD mean arterial pressure was 4-11 mm Hg higher than HS at all points beginning 30 minutes post resuscitation. Cardiac output was significantly higher with HSD vs HS, 1-1.5 l/min difference, at 10 minutes post resuscitation through 3 hours. At 3 minutes post resuscitation, cardiac output was 0.9 l/min greater with HSD, but the difference was not significant. Measured plasma volume was 4.4 ml/kg larger after HSD than HS at 10 minutes post resuscitation, but the difference was not statistically significant. After 3 hours, plasma volume was significantly greater with HSD, 11 ml/kg. The focus of this study was cardiovascular function. The dose given was nearly identical to that used in current clinical trials. The addition of dextran to HS resulted in a more sustained response. A statistically significant difference in cardiac output of over one l/min was apparent at 10 minutes post resuscitation. The difference was attributed to better plasma volume expansion.

2. Maningas, et al. (Letterman Group) "Small volume infusion of 7.5% NaCl/6% dextran 70 for treatment of severe hemorrhagic shock in swine." Annals of Emergency Medicine 15:1131-1137, 1986.

In this study, 60 unanesthetized swine were subjected to a rapid and severe blood loss, 46 ml/kg in 15 minutes, and then resuscitated with 11.5 ml/kg of 0.9% NaCl (NS), 7.5% NaCl (HS), 6% dextran 70 (D) or 7.5% NaCl/6% dextran 70 (HSD). Long term survival was best with HSD (100%), next best with D (69%), followed by HS (53%) and NS (13%). Mean arterial pressure was slightly better (+8 mm Hg) immediately after infusion with HSD vs HS alone, but the difference was not statistically significant. After 15 minutes, arterial pressure with HSD was 20 mm Hg higher than with HS, the difference was significant. Hematocrit changes showed a better initial volume expansion with HSD vs HS immediately after infusion. The focus of this study was long term survival in which HSD was clearly superior. Slightly better initial volume expansion after HSD versus HS was found in this study where 11.5 ml/kg of both fluids were given. This is 3-4 times the typical clinical dose being tested in FDA trials.

3. Velasco, et al. (Sao Paulo Group) "Hypertonic and hyperoncotic resuscitation from severe hemorrhagic shock in dogs. A comparative study." Manuscript submitted to Critical Care Medicine; Abstract published in Circulatory Shock 21:338, 1987.

This group compared the effectiveness of 6 ml/kg of 7.5% NaCl (HS) and 6% dextran 70 (D) each alone and in combination for resuscitation of 42 mongrel dogs in severe hemorrhagic shock, bled volume = 54.2 ± 1.3 ml/kg, shock duration = 30 or 60 minutes. HSD produced the highest survival rate (92%, n = 12), D produced the lowest (58%, n = 12) while HS alone produced an intermediate survival rate (75%, n = 12). Plasma volume expansion was observed with all groups, but was transient in HS alone. At five minutes after resuscitation plasma

volume was almost 5 ml/kg greater with HSD than with HS. Beginning at 5 minutes post resuscitation there were apparent differences in blood pressure and cardiac output; both were higher with HSD. In summary, HSD was superior to HS alone in this animal model which focused on long term survival and cardiovascular function for 3 hour post resuscitation. The differences in arterial pressure and cardiac output during the first 15-30 post infusion were apparent and statistically significant.

4. Walsh, et al. (Davis Group) "Improved resuscitation of hemorrhagic shock after adding high concentrations of dextran 70 to hypertonic saline." Circulatory Shock 21:338-339 (abstract)

In this series of experiments smaller resuscitation volumes (2-3 ml/kg) were used. We reasoned that complete cardiovascular function would not be as easily achieved with this smaller volume and allow a better evaluation of the importance of the colloid in hypertonic saline. Actually this volume is not unlike the actual volumes given in clinical trials. Typical weight range of trauma patients is 60-90 kg and the dose given is 250 ml or 2.7 - 4.2 ml/kg. Unanesthetized sheep were bled for 2 hours to hold arterial pressure at 50 mm Hg (bled volume = 36 ml/kg) and then given 100 ml of either 7.5% NaCl (HS) alone, HS 6% in dextran 70 (HS-6%D) or HS in 24% dextran 70 (HS-24%D). This is the same non-lethal hemorrhage model used in study 1. There were significantly higher cardiac outputs at 15 minutes post resuscitation and greater plasma volume expansion at 10 minutes with HS-6%D versus HS and HS-24%D versus HS-6%D. Figure 3 shows mean cardiac output and arterial pressure. Figure 4 shows hematocrit plotted versus time for the 3 groups. Finally, figure 5 shows individual experiments plotted for dose of dextran versus estimated vascular expansion and cardiac output versus volume expansion. Blood volume expansion was estimated from fall in hemoglobin (Hb) as % expansion = $(Hb_i - Hb_f)/Hb_f$.

A total of 6 and 24 g of dextran were the doses used in these studies of 42 kg sheep. In the patients treated in the current clinical trials, the dose of dextran given is 15 g. When resuscitation with 2.6 ml/kg of HS vs HSD were compared there was an apparent 'dose response' effect of dextran on plasma volume, cardiac output and arterial pressure. In these studies as in the others, the better volume expansion and cardiac outputs during the early post resuscitation period was found in the hypertonic saline/dextran groups.

Table 1 is a summary of all experiments comparing resuscitation with 2400 mosm hypertonic saline (HS) versus hypertonic saline/6% dextran 70 (HSD). Shown are the results of the early effects on plasma volume expansion, cardiac output and arterial pressure. Taken as a whole the data strongly supports the value of the addition of dextran to hypertonic saline resuscitation formulations. In every case dextran caused better volume expansion and higher cardiac output. The key question is: How important is a 5-10 mm Hg difference in arterial pressure or a 0.5-1.0 l/min better cardiac output during the 10-30 minute period before conventional large volume resuscitation begins? I believe the reasonable answer is that for most trauma patients it would not be important, but that in a few critical patients it would make the difference between life and death. Also, it is reasonable to expect that dextran becomes more important as patient transport times increase or follow-up resuscitation is delayed.

Effectiveness of multiple boli resuscitation with hypertonic saline/dextran

The dose for HSD (7.5% NaCl/6% dextran 70) of 4 ml/kg or 250 ml per patient has been found to be effective for treatment of moderate hemorrhage. However, a single fixed volume dose of HSD does not provide for any titration of efficacy. Clearly, some wounded soldiers will require less volume expansions - others will require more. In this study we examined the effectiveness of infusing small single syringe 40 ml boli of HSD given at 15 minute intervals as needed to maintain mean arterial pressure above 70 mm Hg. Results were compared with a control group given 40 ml boli of normal saline and another group given 40 ml boli of a near saturated salt solution (28% NaCl/24% dextran 70).

Resuscitation of conscious sheep was begun after 2 hrs of hemorrhage, bleed volume 30-47 ml/kg. Arterial pressure could not be maintained with 40 ml boli of isotonic saline given at 15 minute intervals, figure 6 shows a representative experiment. However, arterial pressure was

maintained with two to three boli of 7.5% NaCl/6% dextran 70 or a single injection of 28% NaCl/24% dextran 70. Figures 7 and 8 show representative experiments from both groups. Figure 9 shows averaged results from 6 sheep each.

The data show that small multiple boli (~1 ml/kg) of 7.5% NaCl/6% dextran 70 can be safely and effectively used to maintain arterial pressure and cardiac output. In addition, the efficacy of smaller volumes of more concentrated solutions is suggested and merits further investigation.

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TABLE 1.

Early Effects of the Dextran Component of Hypertonic Saline/Dextran

Reference	mins post infusion	dose		Vascular Expansion	Cardiac Output	Arterial Pressure
Smith et al (11)	3-10 min	4 ml/kg	HSD	44.3 ml/kg pl volume	6.1 l/min	91 mmHg
			- HS	39.9 ml/kg	5.2 l/min	91 mmHg
			difference	**+ 4.4 ml/kg**	**+ 0.9 l/min**	**0 mmHg**
Maningas et al (17)	1 min	11.5 ml/kg	HSD	76% expansion*	not measured	103 mmHg
			- HS	50% expansion		95 mmHg
			difference	**+ 26% expansion**		**+ 8 mmHg**
Velasco et al (18) 30 min shock	5 min	6 ml/kg	HSD	62.4 ml/kg pl volume	2.6 l/min/m2	80 mmHg
			- HS	57.5 ml/kg	2.2 l/min/m2	70 mmHg
			difference	**+ 4.9 ml/kg**	**+ 0.4 l/min/m2**	**+ 10 mmHg**
" " 60 min shock	5 min	6 ml/kg	HSD	60.5 ml/kg pl volume	2.7 l/min/m2	70 mmHg
			- HS	55.0 ml/kg	2.3 l/min/m2	64 mmHg
			difference	**+ 5.5 ml/kg**	**+ 0.4 l/min/m2**	**+ 6 mmHg**
Walsh et al (19)	3-10 min	2.6 ml/kg	HSD	26% expansion**	1 51% baseline	90 mmHg
			- HS	17% expansion	1 38% baseline	80 mmHg
			difference	**+ 9% expansion**	**+ 13% baseline**	**+ 11 mmHg**

* % blood volume expansion calculated as (Hct'-Hct")/Hct" , where ' and " represent initial and final values, respectively.

** % blood volume expansion calculated as above except using blood hemoglobin.

Legends for Figures

1. Mean arterial pressure measured in 5 groups of unanesthetized sheep during 1 hour of baseline, 2 hours of hemorrhage and for 2 hours after a 4 ml/kg bolus infusion of 2400 mosm/l solutions of 1) NaCl, 2) NaCl-Na Acetate (0.6/0.6 M) mixture, 3) NaCl-Mannitol (0.7/1.0 M) mixture, 4) Na Bicarbonate or 5) Glucose.

2. Cardiac output in 4 groups of unanesthetized sheep during hemorrhage and after bolus infusion with 4 ml/kg of 1) 2400 mosm/l hypertonic saline, 2) hypertonic saline with 6% dextran 70, 3) 6% dextran 70 in normal saline and 4) no infusion.

3. Mean cardiac output and arterial pressures plotted for hemorrhaged sheep treated with 100 ml of 7.5% NaCl (HS), 7.5% NaCl/6% dextran 70 and 7.5% NaCl/24% dextran 70.

4. Measured hematocrit changes measured in same animals as figure 3.

5. Individual experiments are plotted showing relationship between dose of dextran and initial blood volume expansion. Lines connect experiments conducted on same animal. Also shown is increase in cardiac output plotted versus volume expansion.

6. A representative experiment of a hemorrhaged sheep resuscitated with 40 ml boli infusions of normal saline given every 15 minutes as needed to maintain mean arterial pressure greater than 70 mm Hg. Boli infusions of normal saline were ineffective at maintaining arterial pressure.

7. A representative experiment of a hemorrhaged sheep treated with three 40 ml boli of 7.5% NaCl/6% dextran over 3 hours to maintain arterial pressure above 70 mm Hg.

8. A representative experiment in which only one 40 ml boli of 28.2% NaCl/24% dextran 70 was required to stabilize arterial pressure and cardiac output for 3 hours after a blood loss of 1120 ml.

9. Mean results of cardiac output and arterial pressure of 2 groups of sheep resuscitated with small (~1 ml/kg) boli of 7.5% NaCl/6% dextran 70 or 28.2% NaCl/24% dextran 70.

Fig 1

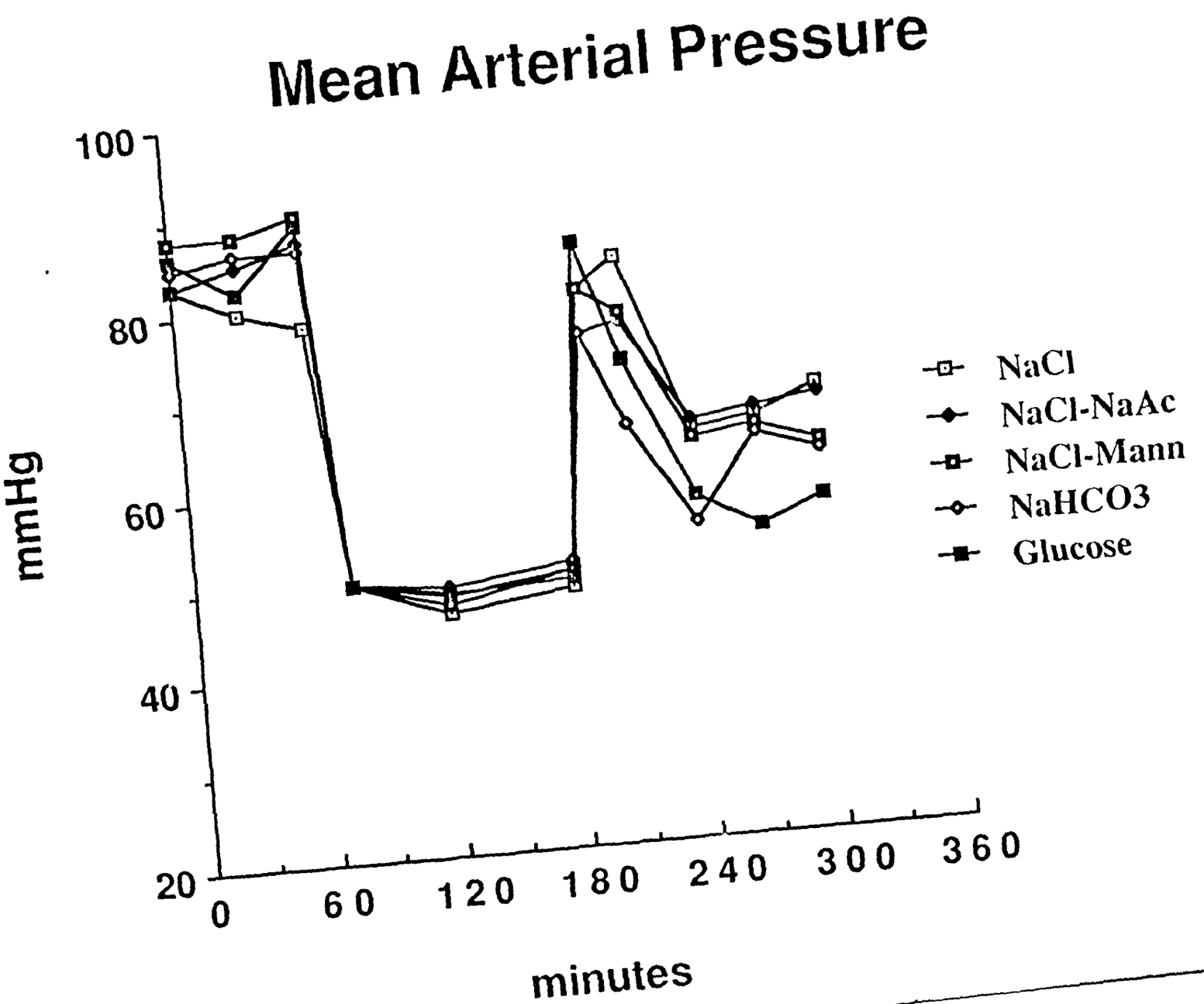
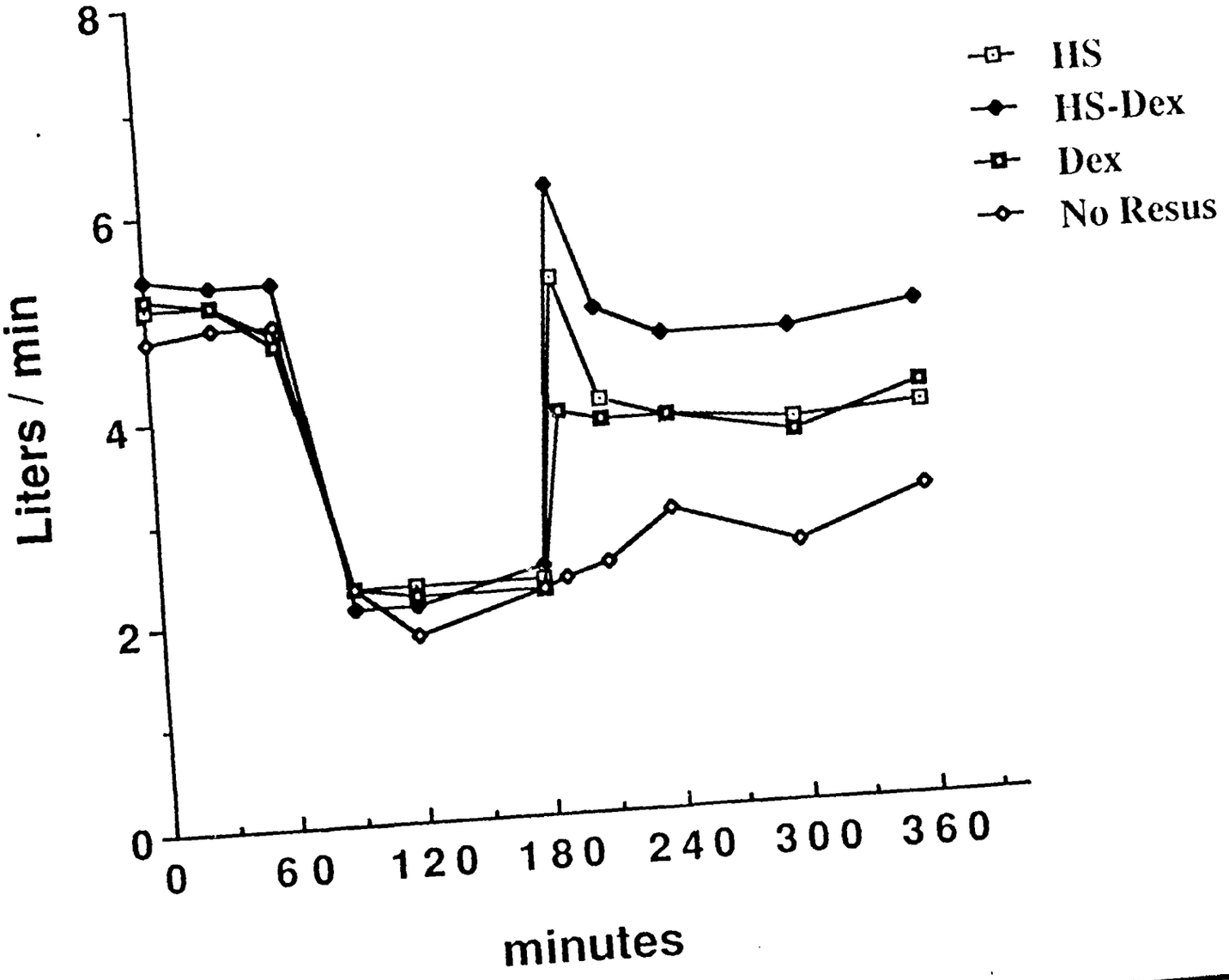
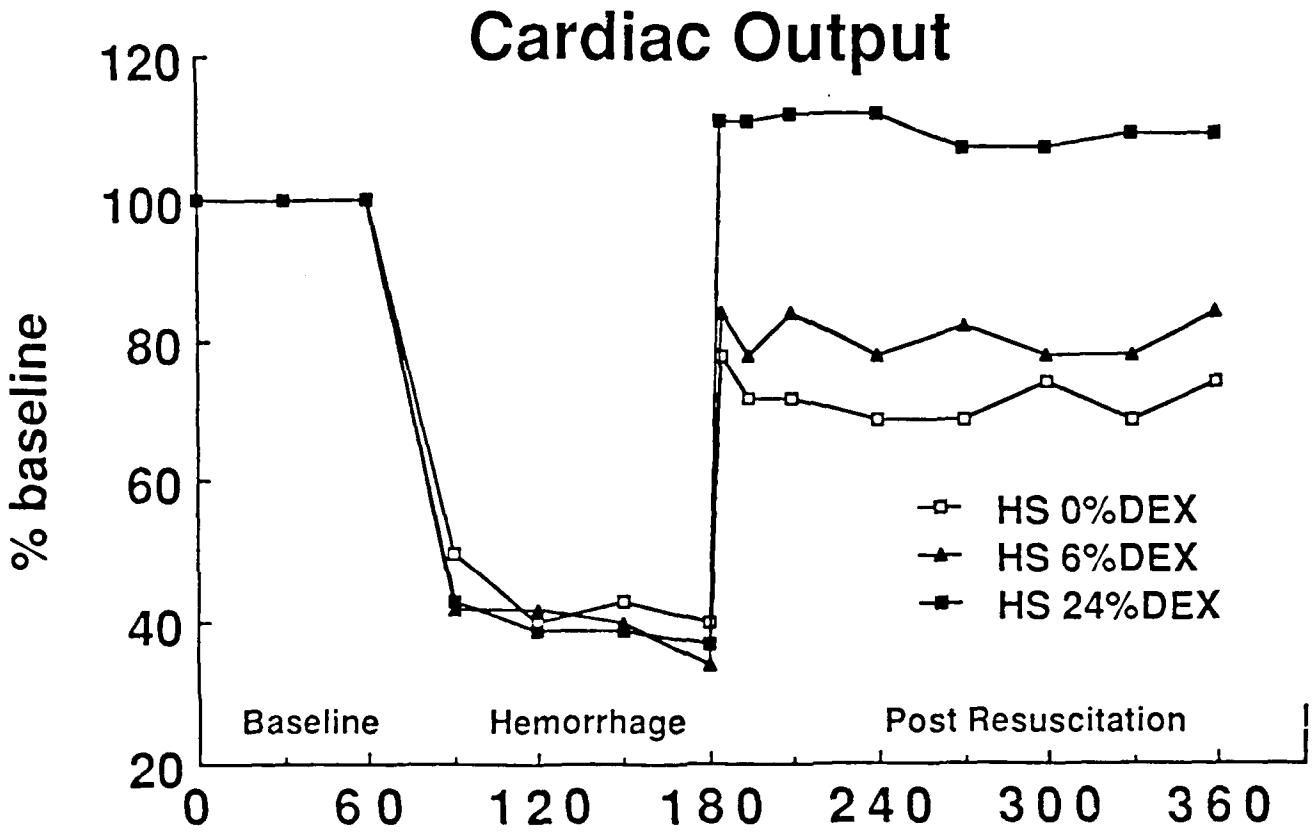

Mean Arterial Pressure
100
80
60
40
20
mmHg
0
60
120
180
240
300
360
minutes
NaCl
NaCl-NaAc
NaCl-Mann
NaHCO3
Glucose

Fig 2

Cardiac Output




Cardiac Output
% baseline
120
100
80
60
40
20
0
60
120
180
240
300
360
Baseline
Hemorrhage
Post Resuscitation
HS 0%DEX
HS 6%DEX
HS 24%DEX

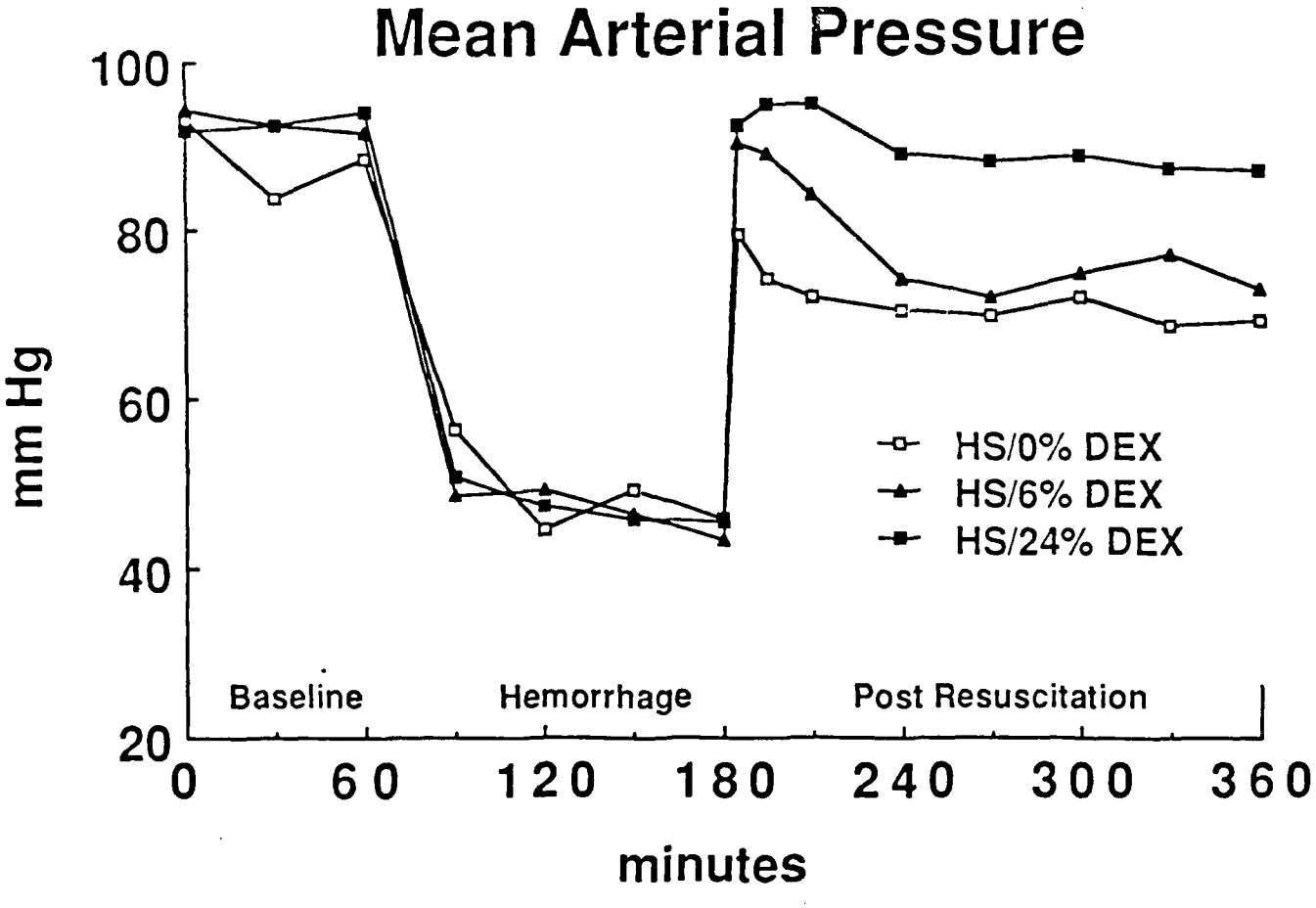

Mean Arterial Pressure
mm Hg
100
80
60
40
20
0
60
120
180
240
300
360
minutes
Baseline
Hemorrhage
Post Resuscitation
HS/0% DEX
HS/6% DEX
HS/24% DEX

Fig 4

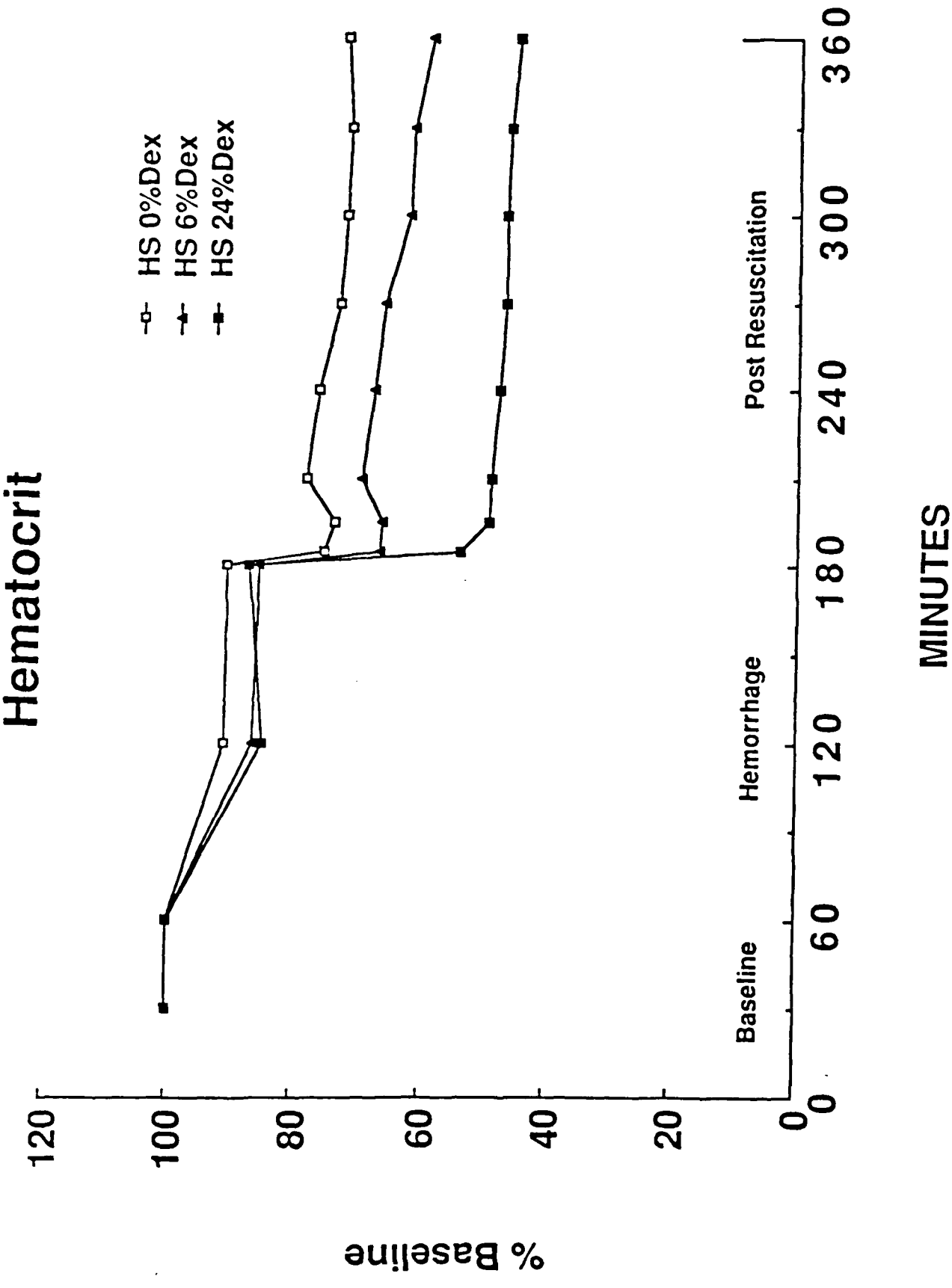
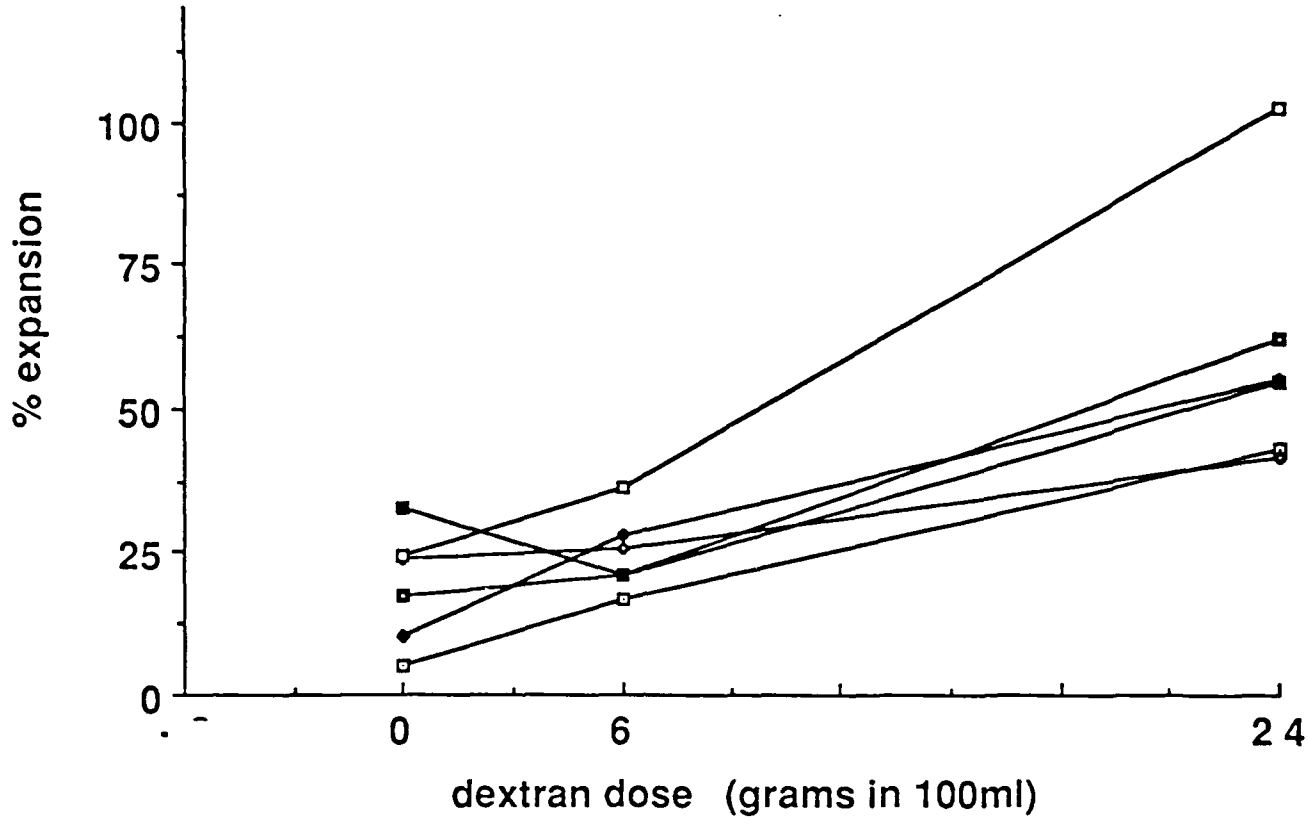
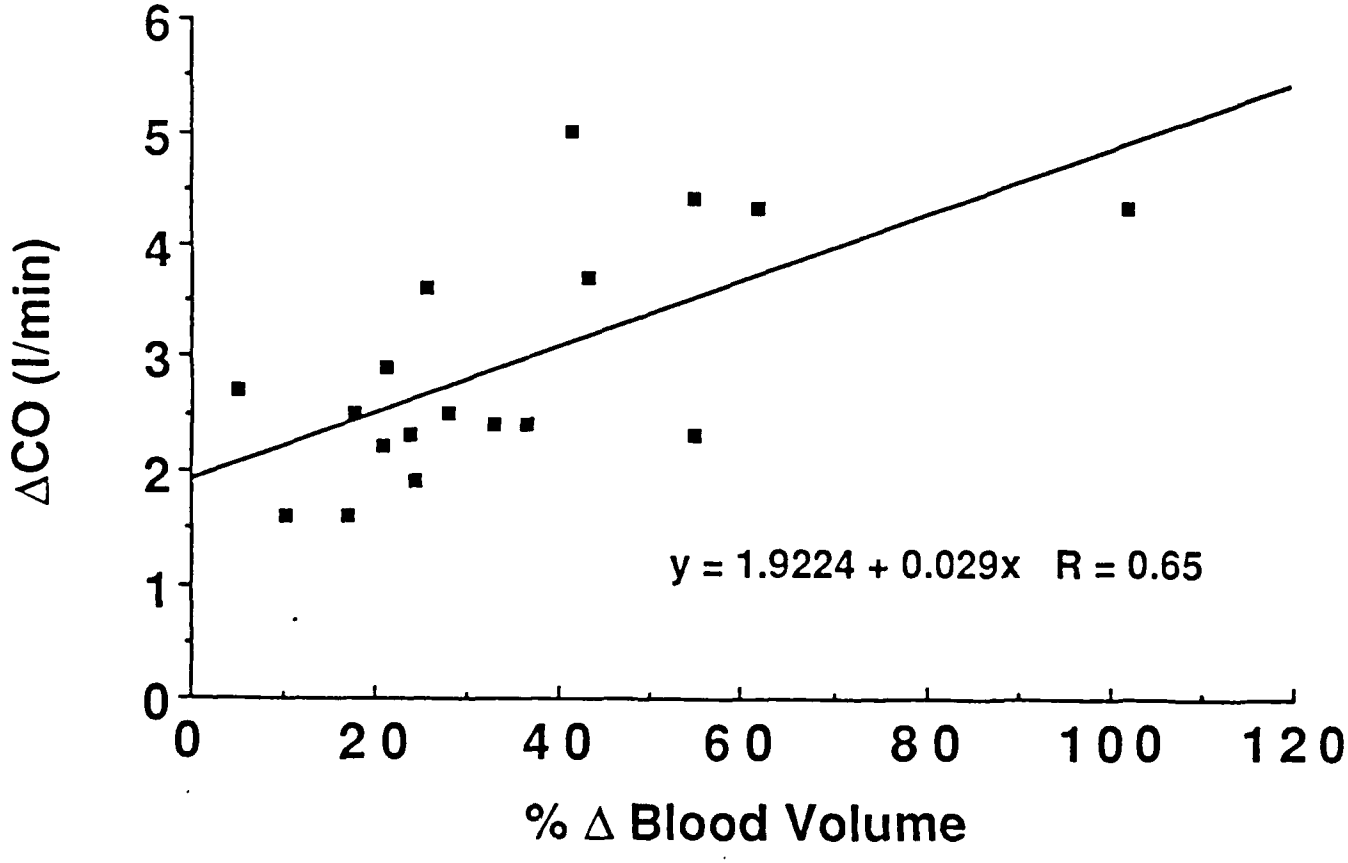

Hematocrit
HS 0%Dex
HS 6%Dex
HS 24%Dex
% Baseline
120
100
80
60
40
20
0
Baseline
Hemorrhage
Post Resuscitation
0
60
120
180
240
300
360
MINUTES

Fig 5

Blood volume expansion vs dextran dose



Cardiac Output vs. Blood Volume Expansion



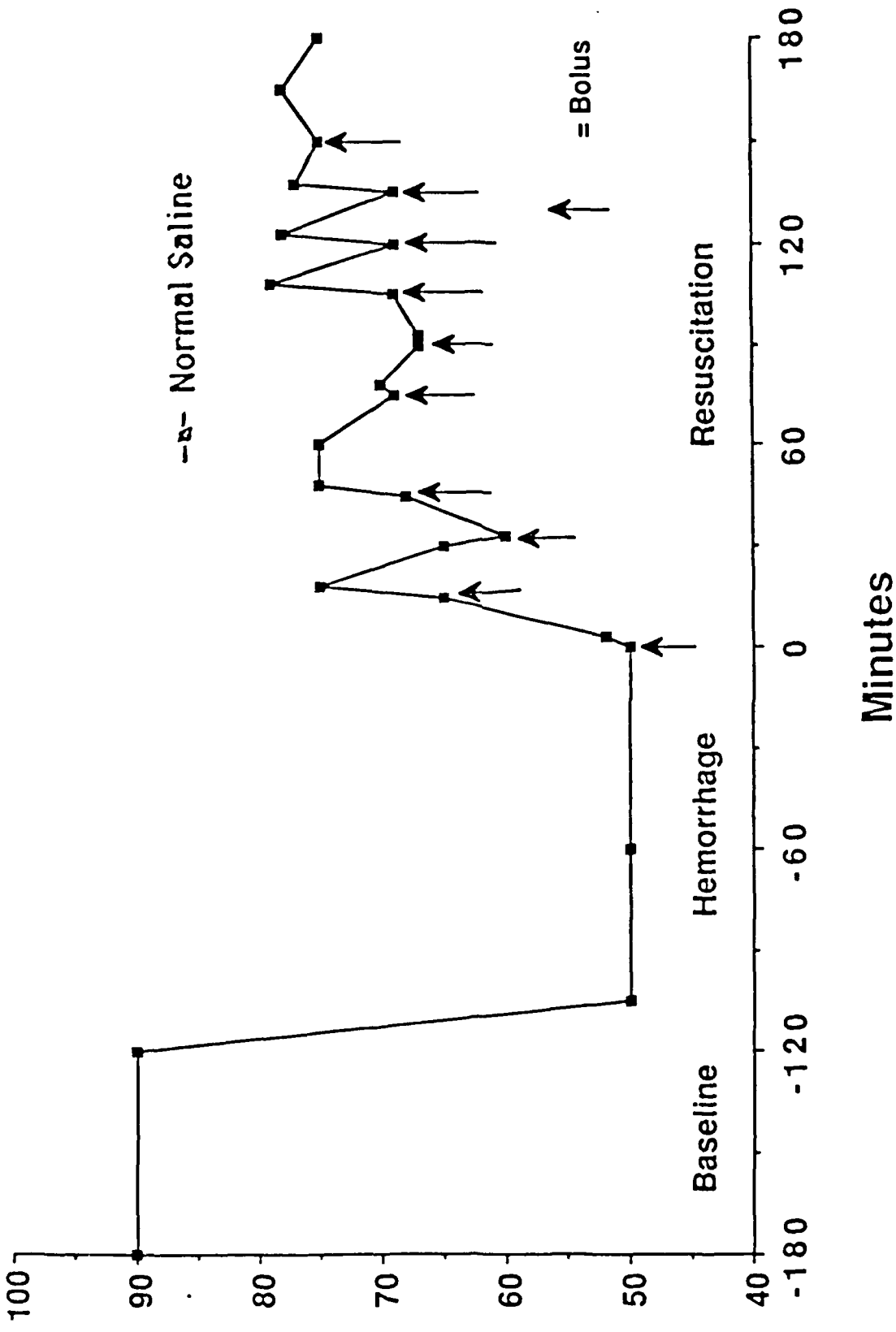

Mean Arterial Pressure
Normal Saline
= Bolus
mmHg
100
90
80
70
60
50
40
-180
-120
-60
0
60
120
180
Minutes
Baseline
Hemorrhage
Resuscitation

Fig 6

Fig 7

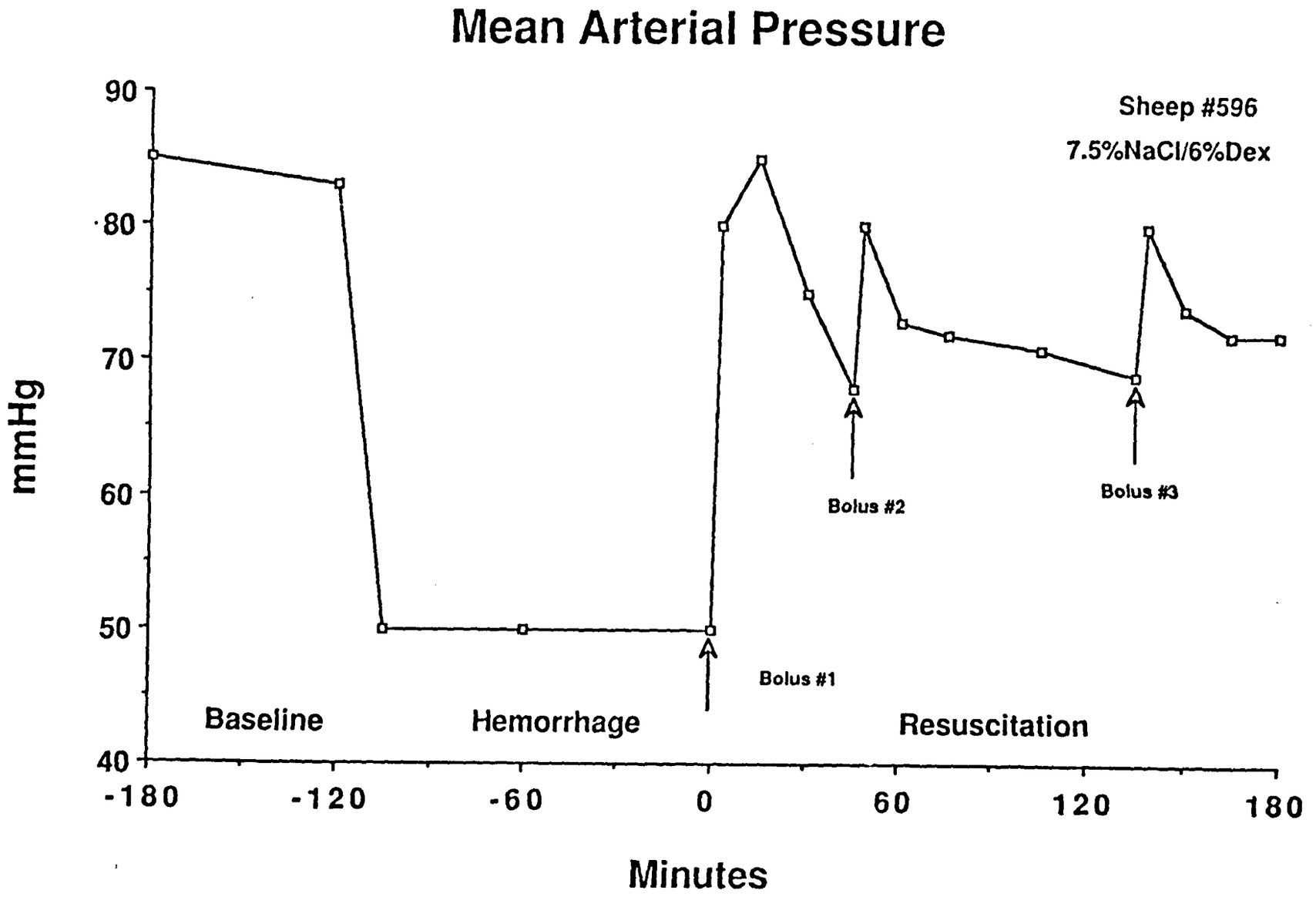
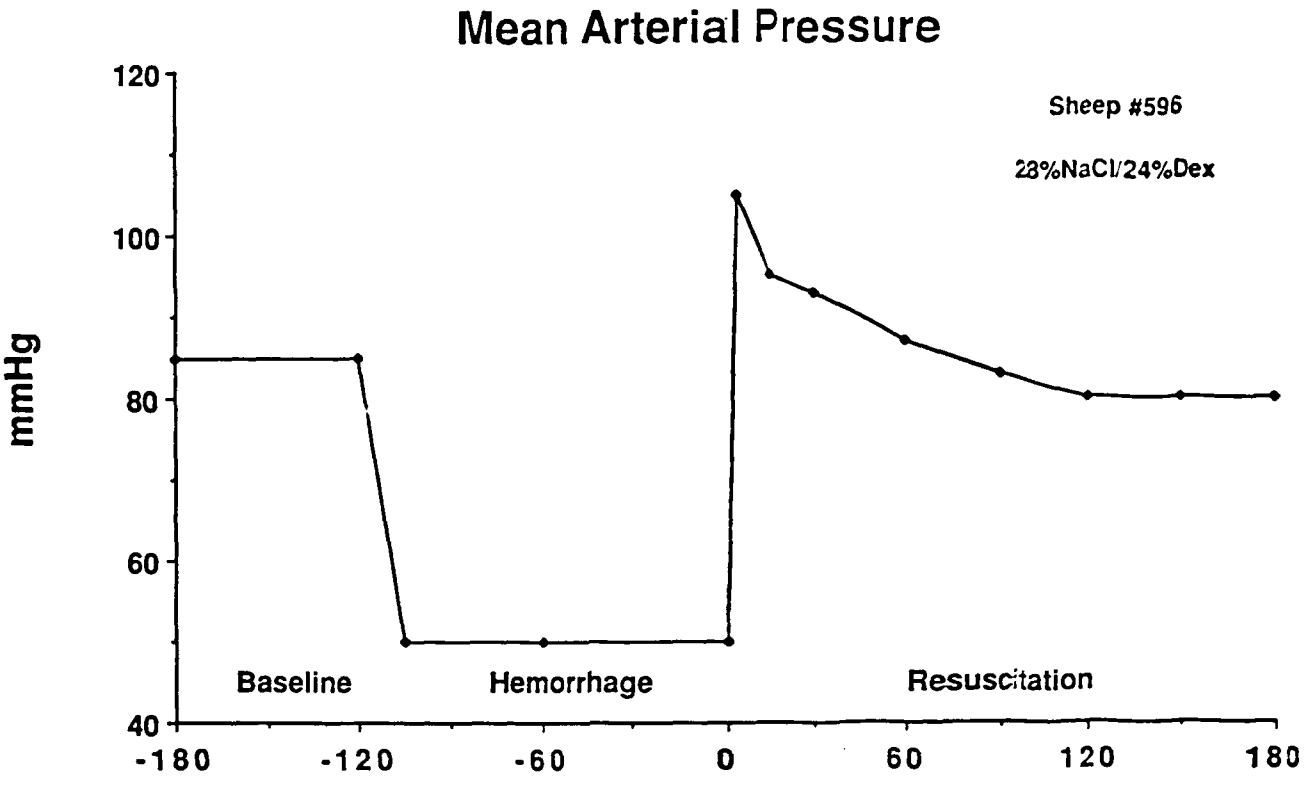
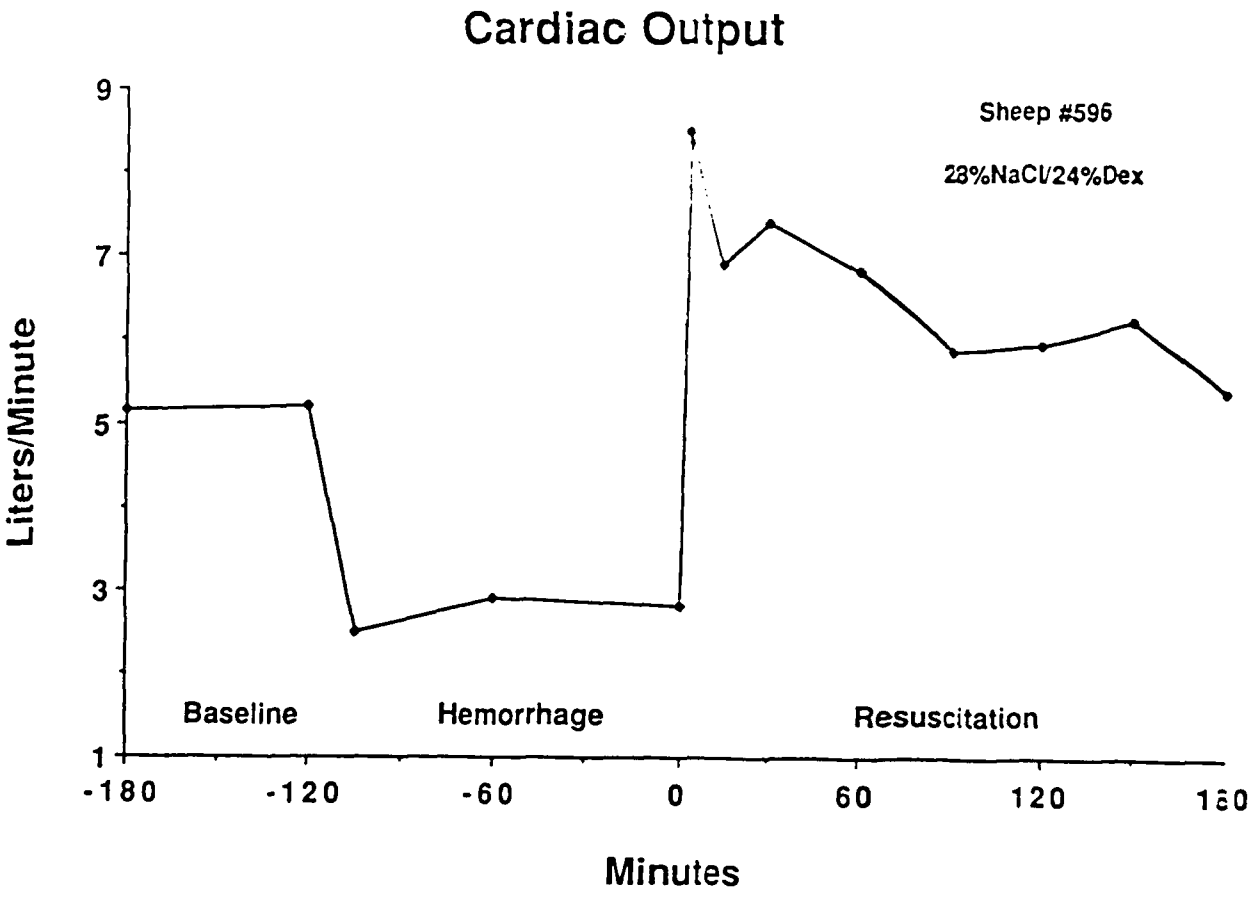
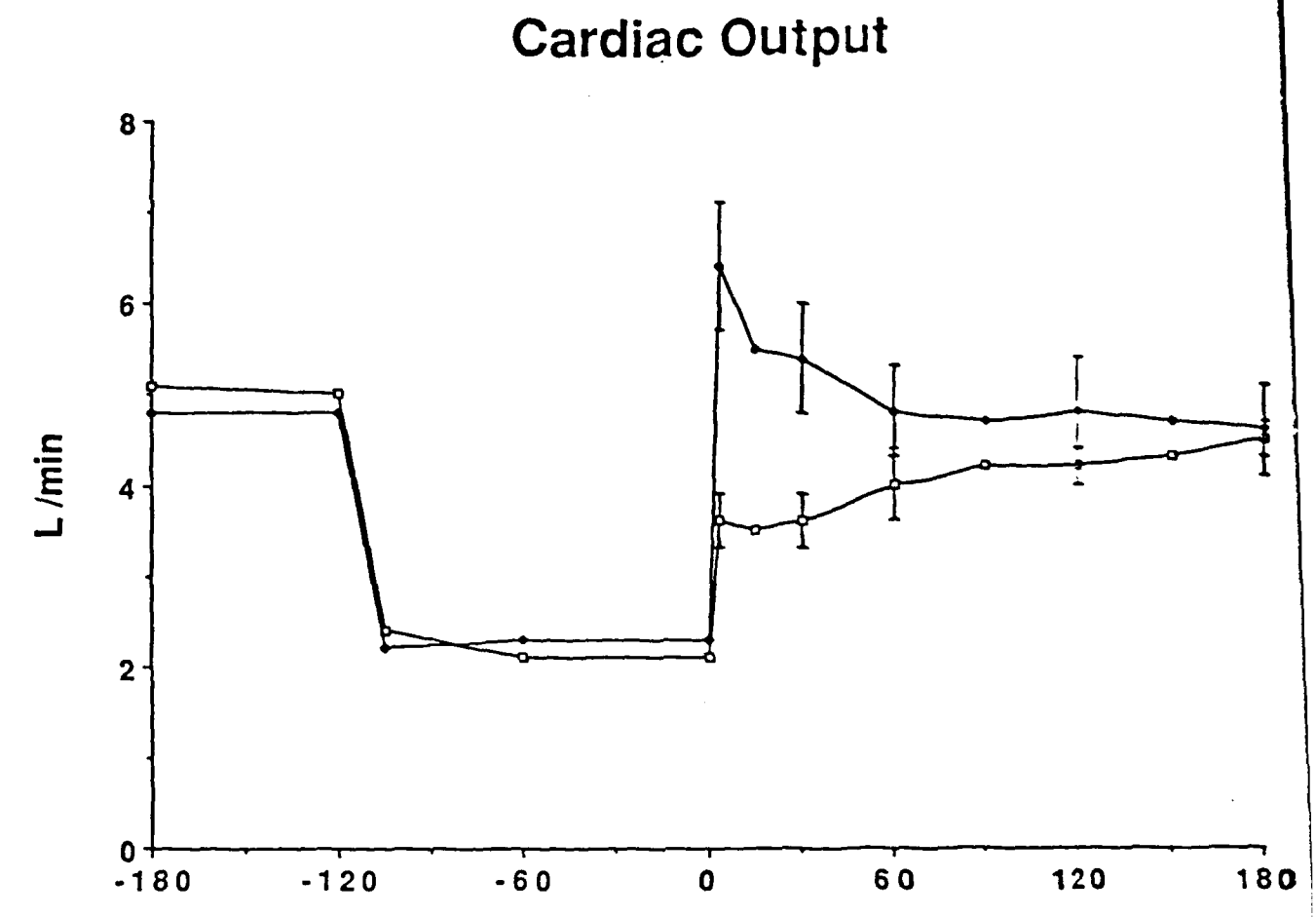
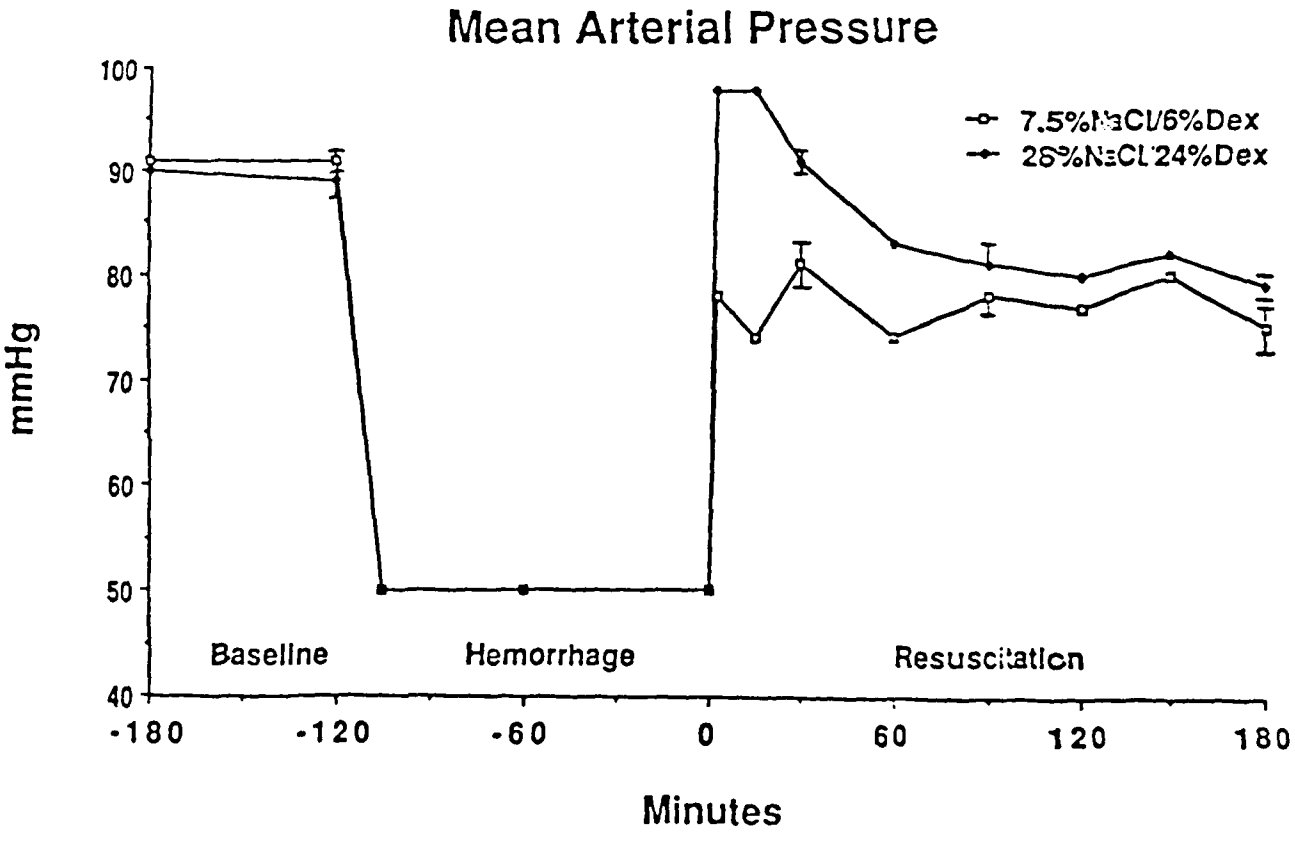

Mean Arterial Pressure
Sheep #596
7.5%NaCl/6%Dex
90
80
70
60
50
40
mmHg
Bolus #1
Bolus #2
Bolus #3
Baseline
Hemorrhage
Resuscitation
-180
-120
-60
0
60
120
180
Minutes

Fig 8


Mean Arterial Pressure
Sheep #596
28%NaCl/24%Dex
mmHg
120
100
80
60
40
Baseline
Hemorrhage
Resuscitation
-180
-120
-60
0
60
120
180


Cardiac Output
Sheep #596
28%NaCl/24%Dex
Liters/Minute
9
7
5
3
1
Baseline
Hemorrhage
Resuscitation
-180
-120
-60
0
60
120
180
Minutes


Cardiac Output
L/min
8
6
4
2
0
-180
-120
-60
0
60
120
180


Mean Arterial Pressure
mmHg
100
90
80
70
60
50
40
7.5%NaCl/6%Dex
Baseline
Hemorrhage
Resuscitation
-180
-120
-60
0
60
120
180
Minutes

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